# Overview

## Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder

Second-tier testing for patients in whom previous targeted gene variant analyses for specific Marfan and related genes were negative

Establishing a diagnosis of a Marfan or a related disorder in some cases, allowing for appropriate management and surveillance for aneurysms and other disease features based on the gene involved

Identifying variants within genes known to be associated with increased risk for aneurysms and other disease features allowing for predictive testing of at-risk family members

## Genetics Test Information

This test includes next-generation sequencing (NGS) and supplemental Sanger sequencing to evaluate for variants in the `ACTA2`, `CBS`, `COL3A1`, `COL5A1`, `COL5A2`, `FBN1`, `FBN2`, `FLNA`, `MFAP5`, `MYH11`, `MYLK`, `NOTCH1`, `PRKG1`, `SKI`, `SLC2A10`, `SMAD3`, `SMAD4`, `TGFB2`, `TGFB3`, `TGFBRI`, and `TGFBRII` genes. Additionally, NGS is used to test for the presence of large deletions and duplications in a subset of genes.

Prior Authorization is available for this assay; see Special Instructions.

## Highlights

This test uses next-generation sequencing with copy number variation analysis to test for variants in the `ACTA2`, `CBS`, `COL3A1`, `COL5A1`, `COL5A2`, `FBN1`, `FBN2`, `FLNA`, `MFAP5`, `MYH11`, `MYLK`, `NOTCH1`, `PRKG1`, `SKI`, `SLC2A10`, `SMAD3`, `SMAD4`, `TGFB2`, `TGFB3`, `TGFBRI`, and `TGFBRII` genes.

This test may aid in the diagnosis of Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysm and dissection (TAAD), or a related disorder.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

## Special Instructions

- Informed Consent for Genetic Testing
- Marfan and Related Disorders Patient Information
- Marfan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions
- Informed Consent for Genetic Testing (Spanish)

## Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing Followed by qPCR and/or Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

## NY State Available

Yes
**Specimen Type**
Varies

**Advisory Information**
Targeted testing for familial variants (also called site-specific or known mutation testing) is available for the genes on this panel. See:

- KVAR1 / Known Variant Analysis-1 Variant, Varies
- KVAR2 / Known Variant Analysis-2 Variants, Varies
- KVAR3 / Known Variant Analysis-3+ Variants, Varies

Call 800-533-1710 to confirm the appropriate test for targeted testing.

**Shipping Instructions**
Specimen preferred to arrive within 96 hours of collection.

**Necessary Information**
1. Marfan and Related Disorders Patient Information (T636) is required, see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

**Specimen Required**
Prior Authorization is available for this test. Submit the required form with the specimen.

Submit only 1 of the following specimens:

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

**Collection Instructions:**
1. Invert several times to mix blood.
2. Send specimen in original tube.

**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated 14 days

**Specimen Type:** DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100mcL (microliters)
Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
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Clinical and Interpretive

Clinical Information

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the \( FBN1 \) gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and mitral valve prolapse and aortic root dilatation/dissection are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of \( FBN1 \). Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the \( FBN1 \) gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve
prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis).

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities, and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants of the SMAD3 gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants of the TGFBR3 gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity.

TAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is ACTA2. For other genes also implicated in TAAD, refer to the table below.

The COL3A1 gene causes Ehlers Danlos syndrome, vascular type (type IV), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously. The COL5A1 and COL5A2 genes cause Ehlers Danlos syndrome, classic type (type I and type II), an autosomal dominant connective tissue disorder characterized by skin hyperextensibility, widened atrophic scars, joint hypermobility, smooth, velvety skin, and easy bruising. The FLNA gene causes FLNA-related periventricular nodular heterotopia (PVNH), an X-linked neuronal migration disorder where the majority of affected individuals are female. This condition is characterized by seizures, hyperflexible joints, and cardiac findings, which include thoracic aortic aneurysm and dissection. Some individuals show clinical overlap with EDS.

Autosomal dominant variants of the FBN2 gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm.

Variants of the CBS gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting.

Variants in the SKI gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS, but, when present, it can be severe.

Homozygous and compound heterozygous loss of function variants in the SLC2A10 gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features.

Variants in the NOTCH1 gene cause aortic valve disease, with individuals displaying a range of aortic valve abnormalities and severe valve calcification.

**Genes included in Marfan Syndrome and Related Disorders Multi-Gene Panel:**

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<th>Protein</th>
<th>Inheritance</th>
<th>Known Association</th>
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<tr>
<td>Gene</td>
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<tr>
<td>ACTA2</td>
<td>Actin, alpha-2, smooth muscle, aorta</td>
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<td>TAAD</td>
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<tr>
<td>CBS</td>
<td>Cystathionine beta-synthase</td>
<td>AR</td>
<td>Homocystinuria</td>
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<td>COL3A1</td>
<td>Collagen, type III, alpha-1</td>
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<td>COL5A1</td>
<td>Collagen, type V alpha-1</td>
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<td>Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II)</td>
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<tr>
<td>COL5A2</td>
<td>Collagen, type V alpha-2</td>
<td>AD</td>
<td>Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II)</td>
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<td>FBN1</td>
<td>Fibrillin 1</td>
<td>AD</td>
<td>Marfan syndrome/TAAD/Ectopia Lenti/ MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome</td>
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<td>FBN2</td>
<td>Fibrillin 2</td>
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<td>Congenital Contractural Arachnodactyly</td>
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<td>FLNA</td>
<td>Filamin A</td>
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<td>Microfibril-associated protein 5</td>
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<td>TAAD</td>
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<td>TAAD</td>
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<td>MYLK</td>
<td>Myosin light chain kinase</td>
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<td>TAAD</td>
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<td>NOTCH1</td>
<td>Notch, drosophila, homolog of, 1</td>
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<td>Aortic valve disease/Adams-Oliver Syndrome</td>
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<td>PRKG1</td>
<td>Protein kinase, cGMP-dependent, type 1</td>
<td>AD</td>
<td>TAAD</td>
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<tr>
<td>SKI</td>
<td>V-SKI avian sarcoma viral oncogene homolog</td>
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<td>Shprintzen-Goldberg syndrome</td>
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<td>AR</td>
<td>Arterial Tortuosity syndrome/TAAD (Autosomal Recessive)</td>
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<td>SMAD3</td>
<td>Mothers against decapentaplegic, drosophila, homolog of, 3</td>
<td>AD</td>
<td>Loeys-Dietz syndrome/TAAD</td>
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### Test Definition: MFRGP

**Marfan and Related Genetic Panel**

<table>
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<th>Gene</th>
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<th>Conditions</th>
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<td>TAAD/JPS/JPS-HHT</td>
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<td>TGFB2</td>
<td>Transforming growth factor, beta-2</td>
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<td>TAAD</td>
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<td>TGFBR1</td>
<td>Transforming growth factor beta receptor, type I</td>
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<tr>
<td>TGFBR2</td>
<td>Transforming growth factor beta receptor, type II</td>
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<td>Loeys-Dietz syndrome/TAAD</td>
</tr>
</tbody>
</table>

**Abbreviations:** Autosomal dominant (AD), autosomal recessive (AR); thoracic aortic aneurysm and dissection (TAAD); juvenile polyposis syndrome (JPS); juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia (JPS-HHT)

**Indications for testing include but are not limited to:**

- Patients who meet clinical diagnostic criteria (Revised Ghent nosology) for Marfan syndrome
- Patients in whom no specific Marfan or related disorder is evident but for whom there is a clear familial component
- Patients whose family history is consistent with TAAD
- Patients with a personal or family history of thoracic aortic aneurysm and/or dissection or a personal or family history of multiple arterial aneurysms

**Reference Values**

An interpretive report will be provided.

**Interpretation**

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Cautions**

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of Marfan syndrome or a related disorder.
Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a family history of Marfan syndrome or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at risk individuals.

Technical Limitations:

Next generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false negative or positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript and/or human genome assembly used for the analysis of this patient's results.

Clinical Reference


Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or qPCR may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing. (Unpublished Mayo method)

The following genes are evaluated in this multigene panel: ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MFAP5, MYH11, MYLK, NOTCH1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, and TGFBR2.

PDF Report

No

Day(s) and Time(s) Test Performed

Wednesday; Varies

Analytic Time

2 weeks after prior authorization approved

Maximum Laboratory Time

4 weeks

Specimen Retention Time

Extracted DNA: 2 months
Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81410

LOINC® Information

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Prior Authorization
Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.